



THE WOMBAT COLLABORATION
**Women and Babies Health and Wellbeing:
Action through Trials**

Designing a protocol for a maternal or perinatal RCT

WORKBOOK

www.wombatcollaboration.net

How to use this workbook

This workbook will guide you through all of the elements of a clinical trial protocol. Details of what should go into each section are given and there is space for you to write the corresponding part for your protocol.

The protocol is divided into headings that approximate those seen in the CONSORT statement. While CONSORT is a guideline for the reporting of randomised controlled trials it is also a good basis for writing a trial protocol. Using this method will also ensure that your protocol can form the basis of your reports, including the final published report.

For each section of your protocol we have included a list of useful references, websites and other resources which you can refer to if you need more information to complete each section.

You can also request assistance with any aspects of your trial from the WOMBAT team using our online form. We have included a copy of that form in the Workshop Resources Folder.

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The CONSORT Checklist

TITLE & ABSTRACT

1. How participants were allocated to interventions (e.g., "random allocation", "randomised", or "randomly assigned").

INTRODUCTION

2. Background

Scientific background and explanation of rationale.

METHODS

3. Participants

Eligibility criteria for participants and the settings and locations where the data were collected.

4. Interventions

Precise details of the interventions intended for each group and how and when they were actually administered.

5. Objectives

Specific objectives and hypotheses.

6. Outcomes

Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of the measurements (e.g. multiple observations, training of assessors etc.)

7. Sample size

How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.

8. Randomization -- Sequence generation

Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification)

9. Randomization -- Allocation concealment

Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.

10. Randomization - Implementation

Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.

11. Blinding (masking)

Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.

12. Statistical methods

Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.

RESULTS

13. Participant flow

Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.

14. Recruitment

Dates defining the periods of recruitment and follow-up.

15. Baseline data

Baseline demographic and clinical characteristics of each group.

16. Numbers analyzed

Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (e.g., 10/20, not 50%).

17. Outcomes and estimation

For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval).

18. Ancillary analyses

Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.

19. Adverse events

All important adverse events or side effects in each intervention group.

DISCUSSION

20. Interpretation

Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.

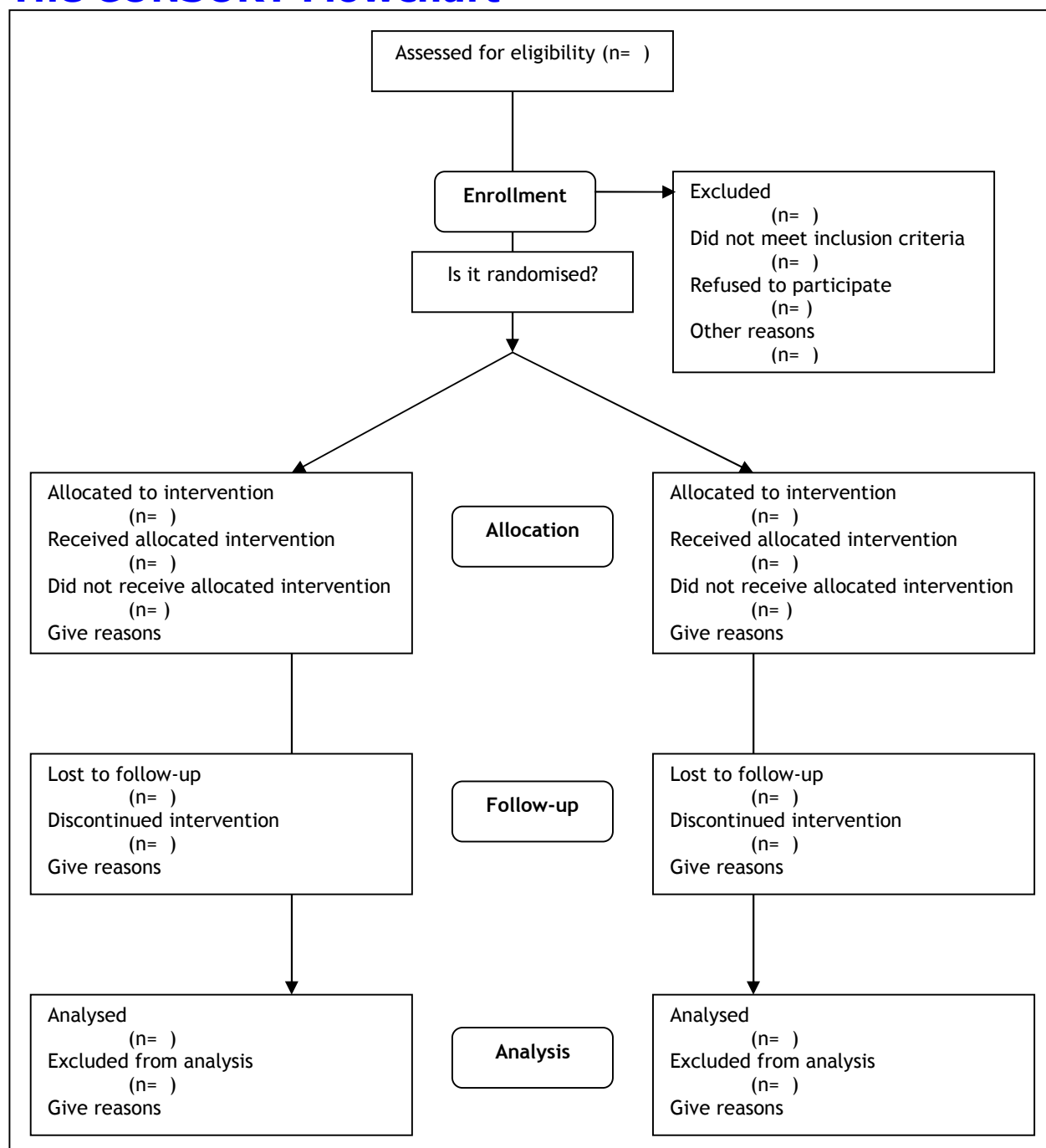
21. Generalizability

Generalizability (external validity) of the trial findings.

22. Overall evidence

General interpretation of the results in the context of current evidence

The CONSORT Flowchart



EXTRA RESOURCES

In the Protocol Workshop Resource Folder

Altman D, Schulz K, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche P, Lang T, for the CONSORT Group. The revised CONSORT Statement for reporting randomized trials: Explanation and Elaboration. *Annals of Internal Medicine* 2001; **134**: 663-694.

Copy of the CONSORT Checklist and CONSORT E-Flowchart

Web links

The CONSORT Statement, Checklist, E-Flowchart and CONSORT for cluster randomised trials are available from the CONSORT website. CONSORT for other trial designs are in preparation.
www.consort-statement.org

PICO Worksheet

PICO: Participant, Intervention, Comparator, Outcome

Use this worksheet to help you formulate your research question.

We have included a worked example to assist you.

<p>Clinical problem: what is it you want to investigate or study? <i>eg. Is progesterone a good thing for preterm birth?</i></p>
<p>Participant Define disease/condition</p> <ul style="list-style-type: none">➤ Severity, stages of condition➤ Setting (hospital, community)➤ Age range, Gestation➤ Other illnesses➤ Exclusions? <p><i>eg. Women with a previous preterm birth <37 weeks</i></p>
<p>Intervention Define intervention</p> <ul style="list-style-type: none">➤ Dose, duration, frequency, route➤ Drugs- any in a class?➤ Define optional and essential elements of the intervention (who must, how must it be done) <p><i>eg. Vaginal progesterone, 100mgs daily, 20 weeks -37 wks</i></p>

<p>Comparator</p> <p>Specify the comparator</p> <ul style="list-style-type: none"> ➤ Placebo ➤ Nothing ➤ Usual care ➤ Other intervention - best evidenced based alternative <p>eg. <i>Placebo</i></p>
<p>Outcomes</p> <ul style="list-style-type: none"> ➤ What outcomes are important, and to whom? ➤ Have scales or measurement tools been validated? ➤ Use of surrogate outcomes-related to the “real outcome” ➤ Primary vs secondary <p>eg. <i>Neonatal RDS, safety outcomes, maternal emotional well-being, cost</i></p>
<p>Now try to frame your question as a testable hypotheses based on PICO</p> <p><i>eg. In women with a previous preterm birth less than 37 weeks (P), does antenatal administration of vaginal progesterone, 100mgs daily, from 20 to 37 weeks gestation (I), compared with placebo (C) reduce neonatal respiratory distress by 30% from 15% to 10% (O)</i></p>

TRIAL PROTOCOL OUTLINE

1. TITLE

The title should state that this is a randomised controlled trial.

It is best to avoid terminology such as double-blind as this can be interpreted in a number of ways.

You should usually have a full title and a short title – the full title should include study design, medicinal product(s) or interventional device if used, nature of treatment, comparators and/or placebo, indication, patient population and setting

The title should be the same across all documents related to the trial

The short title is often an acronym of the long title which is easier to say and remember. Clinical trial registers often also require a lay title.

CONSORT CHECKLIST

Criteria 1: TITLE & ABSTRACT

1. How participants were allocated to interventions (e.g., "random allocation", "randomised", or "randomly assigned").

YOUR DRAFT PROTOCOL

1. TITLE

Title based on PICO

Acroynm

Lay title

2. SUMMARY

The summary should be one to two pages and include the following headings but is best written after the protocol is completed.

We suggest that the summary follow the format below which is based on the information required by the Australian Clinical Trials Registry for registering a trial. It is also consistent with the World Health Organization (WHO) trial registration data set.

Public title (lay title)

Study title in PICO format

Title acronym

Health condition(s) to be studied

Description of intervention(s) and control treatment

Primary outcome

Key secondary outcome/s

Key inclusion and exclusion criteria

Study type

Purpose of study

Allocation to intervention (including details of sequence generation and allocation concealment)

Blinding status

Control group (placebo or active treatment)

Assignment (parallel, cross-over, cluster, other)

Anticipated start date

Target sample size

Funding sources

Primary sponsor/s

Secondary sponsor/s

Ethics approval

EXTRA RESOURCES

In the Protocol Workshop Resource Folder

ACTR Trial registration form

WHO Trial Registration Data Set (data must be entered online)

Example of a trial registered with the ACTR which meets the WHO requirements

Web links

International Clinical Trials Registry Platform (ICTRP)

http://www.who.int/ictrp/data_set/en/index1.html

Australian Clinical Trial Registry

<http://www.actr.org.au/>

3. AIMS

Research outcome

Key questions to be answered

You should consider: (from Guyatt 2006)

- whether there is sufficient doubt about the answer
- what is the burden of illness?
- do the relevant clinical, research and lay communities think that there is a problem?
- what is the potential economic impact of resolving the question?
- what are the costs of conducting the research relative to the potential health and economic benefits?
- is the question in fashion?
- if the question has not been definitively answered, is it the next logical step?

Health impact

- implications from study outcome
- potential impact
- how will this impact be achieved?

EXTRA RESOURCES

In the Protocol Workshop Resource Folder

Guyatt G. Preparing a research protocol to improve chances for success. *Journal of Clinical Epidemiology* 2006; 59:893-899.

Hayes RB. Forming research questions. *Journal of Clinical Epidemiology* 2006; 59:881-886.

Tugwell P, McGowan J. Finding information about the burden of disease. *Journal of Clinical Epidemiology* 2006; 59:887-892.

RESEARCH IMPACT

Rating scale for research impact from the Research Quality Framework

Rating Description

A Adoption of the research has produced an outstanding social, economic, environmental and/or cultural benefit for the wider community, regionally within Australia, nationally or internationally.

B Adoption of the research has produced a significant social, economic environmental and/or cultural benefit for the wider community, regionally within Australia, nationally or internationally.

C Research has been adopted to produce new policies, products, attitudes, behaviours and/or outlooks in the end user community.

D Research has engaged with the end user community to address a social, economic, environmental and/or cultural issue regionally within Australia, nationally or internationally.

E Research has had limited or no identifiable social, economic, environmental and/or cultural outcome, regionally within Australia, nationally or internationally.

Source: Research Quality Framework. Assessing the quality and impact of research in Australia. Recommended RQF. Canberra: Commonwealth of Australia, 2006.

YOUR DRAFT PROTOCOL

3. AIMS

Research outcome

YOUR DRAFT PROTOCOL

3. AIMS continued...

Health impact

Your notes

4. SPECIFIC OBJECTIVES and HYPOTHESES

List study objectives.

Describe purpose of trial in terms of hypothesised effect(s) on primary measure(s) of outcome.

Each objective should be addressed in the final results so consider this at the planning stage.

It is not essential to have separate objectives and hypotheses, provided that the description of outcomes is clear and sufficiently detailed.

CONSORT CHECKLIST
Criteria 5. Objectives
Specific objectives and hypotheses.

EXTRA RESOURCES

In the Protocol Workshop Resource Folder

Gebski V, Marschner I, Keech A. Specifying objectives and outcomes for clinical trials. *MJA* 2002; 176: 491-492.

YOUR DRAFT PROTOCOL

4. SPECIFIC OBJECTIVES AND/OR HYPOTHESES

5. BACKGROUND

Problem statement

- what is the current situation?
- what needs to be done?

Problem description

- who? how? where? when?
- what are the causes?
- what has been done in past?
- what is known about the problem?

Justification

- how might the proposed intervention work – at a biological and clinical level? i.e. what are the *mechanisms* by which the intervention might work
- timeliness - current and timely?
- magnitude
- severity - life threatening/serious morbidity?
- relevance - relate to ongoing problems?
- implications - broad health, social, economic, political issues?
- wide interest
- previous research
- savings/trade-offs
- feasibility
- potential for prevention or containing?

Don't forget to reference this section accurately and to support statements with current references

CONSORT CHECKLIST
Criteria 2. Background
Scientific background and
explanation of rationale.

EXTRA RESOURCES

Examples of problem statements

Example 1: preterm rupture of the membranes

What is the current situation?

There is wide variation in practice in the care of women with preterm prelabour rupture of the membranes between 34 and 37 weeks gestation.

What should be done?

We should know which care options are best for women with this problem.

Example 2: periodontal health and preterm birth

What is the current situation?

Gum disease and periodontal disease may increase the risk of a women giving birth preterm. There has been insufficient assessment of whether dental health preventative strategies during pregnancy may reduce the risk of preterm birth.

What should be done?

Possible strategies require rigorous assessment.

YOUR DRAFT PROTOCOL

5. BACKGROUND

Problem definition and justification

Problem statement

Problem description

5. BACKGROUND continued...

Justification

Your notes

6. DESIGN

Intervention study

Clear description and justification of the type of design (parallel, cross-over, cluster)

CONSORT CHECKLIST

Criteria 13. Participant flow

Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.

Trial flowchart

It is usually helpful to create a schematic showing how the trial will run – trial design, procedures, stages and data collection (see example in Extra Resources below)

EXTRA RESOURCES

In the Protocol Workshop Resources Folder

See Figure 1 HATCH Trial Flowchart from the HATCH Trial Protocol

Cyna A, Andrew M, Robinson J, Crowther C, Baghurst P, Turnbull D, Wicks G, Whittle C. Hypnosis Antenatal Training for Childbirth (HATCH): a randomised controlled trial (NCT00282204). *BMC Pregnancy and Childbirth* 2006; 6:5.

See Trial profile from Zinc supplementation trial follow-up report

Hamadani J, Fuchs G, Osendarp S, Huda S, Grantham-McGregor S. Zinc supplementation during pregnancy and effects on mental development and behaviour of infants: a follow-up study. *Lancet* 2002; 360: 290-294.

YOUR DRAFT PROTOCOL

6. DESIGN

Intervention study

7. PARTICIPANTS

Participant selection

- source of participants (where they come from and why appropriate)
- number of centres involved
- expected number of eligible participants per year and proportions expected to agree to participate

CONSORT CHECKLIST

Criteria 3. Participants
Eligibility criteria for participants and the settings and locations where the data were collected.

Inclusion and exclusion criteria

Inclusion and exclusion criteria with justifications

(e.g. contraindications to trial treatments, incompatible current treatments, recent involvement in other research)

EXTRA RESOURCES

Extract from the CONSORT Statement explanatory notes

(<http://www.consort-statement.org/Statement/examples3a.htm>)

Explanation

Every RCT addresses an issue relevant to some population with the condition of interest. Trialists usually restrict this population by using eligibility criteria and by performing the trial in one or a few centers. Typical selection criteria may relate to age, sex, clinical diagnosis, and comorbid conditions; exclusion criteria are often used to ensure patient safety. Eligibility criteria should be explicitly defined. If relevant, any known inaccuracy of patients' diagnoses should be discussed because it can affect the power of the trial (1).

Careful descriptions of the trial participants and the setting in which they were studied are needed so that readers may assess the external validity (generalizability) of the trial results. Of particular importance is the method of recruitment, such as by referral or self-selection (for example, through advertisements). Because they are applied before randomization, eligibility criteria do not affect the internal validity of a trial, but they do affect the external validity.

1. Rodgers A, MacMahon S. Systematic underestimation of treatment effects as a result of diagnostic test inaccuracy: implications for the interpretation and design of thrombolysis trials. *Thromb Haemost.* 1995;73:167-71.

YOUR DRAFT PROTOCOL

7. PARTICIPANTS

Selection

Source of participants

Number of centres involved

Inclusion criteria

7. PARTICIPANTS continued...

Exclusion criteria

Participation estimates

Your notes

8. INTERVENTION AND COMPARATOR

Detail treatment regimens of both groups

- how and when to be administered

Blinding of treatment groups?

Follow-up schedule

Participant adherence with treatment schedule

- procedures for monitoring
- recording patient adherence information (what, when, where)
- follow-up of non-adherents

Participant withdrawal from trial

- under what circumstances and how will participants be withdrawn from trial
- documentation to be completed on participant withdrawal (including reasons for withdrawal and follow-up information)
- whether and how participants would be replaced

Enough details should be provided that the treatments could be replicated by another investigator

CONSORT CHECKLIST
Criteria 4. Interventions
Precise details of the interventions intended for each group and how and when they were actually administered.

EXTRA RESOURCES

For trials involving administration of drug products:

From the University College London Hospitals “Guide to clinical trial protocol content and format”

General information to include

- full name, generic name and licensed Australian trade name,
- licence information,
- TGA Data Sheet or equivalent,
- summary of known and potential side effects and risks and benefits to human subjects

Use within trial

- description and justification for proposed route of administration, dosage and treatment period
- detail of who administers product (patient, nurse, doctor, carer)
- invasive/radioactive treatments
- dosage form, packaging and labelling of products
- dispensing records, accountability and disposal procedures during trial
- who will supply product
- shelf life, arrangements for storage
- arrangements for continuation of treatment for study patients after end of trial
- other medications permitted during trial including rescue medication and possible interactions or effects that could confound results/conclusions

YOUR DRAFT PROTOCOL

8. INTERVENTION AND COMPARATOR

Intervention

Comparator

8. INTERVENTION AND COMPARATOR continued...

Adherence with treatment schedules

Participant withdrawals

Your notes

9. RCT METHODS

Method of randomisation

- type of randomisation
 - o individual patient or cluster?
 - o simple, block, minimisation including block sizes and if they will vary
 - o allocation ratio – i.e. equal or unequal allocation between treatment arms?
- how will randomisation be implemented?
 - o who, where, how

Allocation concealment

Method of allocation concealment eg. sealed opaque sequentially numbered envelopes, central telephone randomisation, computer randomisation etc.

Stratification

variables to be used for stratification with justification

Blinding

- measurements to be blinded
- who will be blinded?
 - o participants, investigators, outcome assessors
- how will blinding be implemented?
- how will success of blinding be evaluated?

☑ CONSORT CHECKLIST

Criteria 8. Randomization -- Sequence generation

Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification)

Criteria 9. Randomization -- Allocation concealment

Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.

Criteria 10. Randomization - Implementation

Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.

Criteria 11. Blinding (masking)

Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.

EXTRA RESOURCES

In the Protocol Workshop Resource Folder

Beller E, GebSKI V, Keech A. Randomisation in clinical trials. *MJA* 2002;177:565-567.

Altman D, Bland M. Statistics notes: Treatment allocation by minimisation. *BMJ* 2005;330:843.

Altman D, Schulz K. Statistics notes: Concealing treatment allocation in randomised trials. *BMJ* 2001;323:446-447.

Forder P, GebSKI V, Keech A. Allocation concealment and blinding: when ignorance is bliss. *MJA* 2005; 182:87-89.

Bland M, Kerry S. Trials randomised in clusters. *BMJ* 1997; 315:600.

Campbell M. Extending CONSORT to include cluster trials. *BMJ* 2004; 328:654-655.

Medical Research Council. Cluster randomised trials: methodological and ethical considerations. MRC clinical trials series. London: MRC, 2002.

Web links

Cross-over trials and n-of-1 designs

http://symptomresearch.nih.gov/chapter_6/index.htm

JM Bland, BK Butland, JL Peacock, J Poloniecki, F Reid, P Sedgwick. [Statistics Guide for Research Grant Applicants](#) available at:

http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/guide.cfm

YOUR DRAFT PROTOCOL

9. RCT METHODS

Method of randomisation

Allocation concealment

9. RCT METHODS continued...

Stratification

Blinding

Your notes

10. OUTCOMES

Primary study outcome(s)

- most important outcome
- outcome used for sample size calculation

Secondary outcomes

- other outcomes of interest such as clinical, economic, psychosocial outcomes
- may also be adverse events

**Consider carefully use of composite outcomes or surrogate outcomes

How will outcomes be defined?

- international definitions?
- national definitions?
- standardised definitions?

CONSORT CHECKLIST

Criteria 6. Outcomes

Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).

EXTRA RESOURCES

In the Protocol Workshop Resource Folder

Gebski V, Marschner I, Keech A. Specifying objectives and outcomes for clinical trials. *MJA* 2002; **176**:491-492.

Montori V, Permyer-Miralda G, Ferreira-Gonzalez I, Busse J, Pachecho-Huergo V, Bryant D, Alonso J, Akl E, Domingo-Salvany A, Mills E, Wu P, Schunemann H, Jaeschke R, Guyatt G. The validity of composite endpoints in clinical trials. *BMJ* 2005; **330**: 594 - 596.

Johnson A. Randomised controlled trials in perinatal medicine: 3. Identifying and measuring endpoints in randomised controlled trials. *BJOG* 1997; **104**:768-771.

Grimes D, Schulz K. Surrogate end points in clinical research: hazardous to your health. *Obstetrics & Gynecology* 2005; **105**:1114-1118.

Examples of definitions from the ACTS trial of vitamin C and E for preeclampsia

Preeclampsia: hypertension occurring with one or more of the following

- proteinuria: ≥ 300 mg of protein per 24 hours or a ratio of protein to creatinine of ≥ 30 mg per millimole in a "spot" urine specimen
- renal insufficiency: a serum or plasma creatinine level ≥ 0.09 mmol per liter (≥ 1.02 mg per deciliter)
- oliguria (<30 ml of urine per hour for ≥ 6 hours)

Liver disease: aspartate aminotransferase or alanine aminotransferase level of >50 IU per liter, severe epigastric or right-upper-quadrant pain, or both

Neurologic problems: convulsions(eclampsia); hyperreflexia with clonus; severe headaches with hyperreflexia or persistent visual disturbances (scotomata)

Haematologic disturbances

- thrombocytopenia: platelet count of <100,000 per cubic millimeter
- disseminated intravascular coagulation: INR of >1.5, an activated partial-thromboplastin time >5 seconds longer than the laboratory reference value, or a fibrinogen level of <1 g per liter;
- hemolysis: lactate dehydrogenase level >500 IU per liter, fragmentocytes on peripheral-blood smear, or both

Fetal growth restriction: birth weight below the 10th percentile for gestational age.

Rumbold A, Crowther C, Haslam R, Dekker G, Robinson J, for the ACTS Study Group. Vitamins C and E and the risks of preeclampsia and perinatal complications. *NEJM* 2006; **354**: 1796 - 1806.

YOUR DRAFT PROTOCOL

10. OUTCOMES

Primary outcome measures

Secondary outcome measures

10. OUTCOMES continued...

Descriptive comparisons

Additional data collected

Your notes

11. SAMPLE SIZE CALCULATION

Estimate incidence of primary outcome measure(s)

Estimate expected change with intervention

Set desired confidence levels

p value (alpha)

power (beta)

Calculate required sample size

- Estimate recruitment rate
- Estimate adjustment for anticipated losses to follow-up.

CONSORT CHECKLIST

Criteria 7. Sample size

How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.

EXTRA RESOURCES

Power calculations

From the University College London Hospitals “Guide to clinical trial protocol content and format”

Details of the power calculation used to estimate required sample size for primary outcome

- estimates used (size of clinically important effect, drop-out/non-compliance)
- assumptions made (e.g. assumptions of normality)
- relevant justification (i.e. appropriate references or clinical arguments)
- allowance for planned subgroup analyses
- chosen level of significance and power
- methods/formula/software used

Estimate recruitment period for trial (calculated based on expected number of eligible and recruited participants available per year) with justification that required sample size will be attained in practice.

In the Protocol Workshop Resource Folder

Kirby A, GebSKI V, Keech A. Determining the sample size in a clinical trial. *MJA* 2002; **177**:256-257.

Tarnow-Mordi W, Brocklehurst P. Randomised controlled trials in perinatal medicine: 1. The need for studies of mortality and major morbidity with adequate power. *BJOG* 1997; **104**:763-765.

Kerry S, Bland M. Statistics notes: Sample size in cluster randomisation. *BMJ* 1998;**316**: 54.

Keech A, GebSKI V. Managing the resource demands of a large sample size in clinical trials: can you succeed with fewer subjects? *MJA* 2002;**177**:437-439.

Cakir B, GebSKI V, Keech A. Flow of participants in randomised studies. *MJA* 2003; **178**:347-349.

Web resources - Sample size calculators

<http://stat.ubc.ca/~rollin/stats/ssize/index.html>

Asher's sample size calculator (for proportions) (can be sensitive to firewalls)

<http://www.chip.org/~asher/calcs/ssc.html>

Epi-Info is a software program to manage data which can be downloaded free from the US Centres for Disease Control - it has a sample size calculator

<http://www.cdc.gov/EpiInfo/>

YOUR DRAFT PROTOCOL

11. SAMPLE SIZE

Incidence of primary outcome measure(s)

Expected change with intervention

Confidence levels, p-value and power

Required sample size

Estimated recruitment rate

Adjustment for anticipated losses to follow-up

12. RECRUITMENT

Participant recruitment

- method of recruitment (e.g. adverts, clinics etc.)
- payment of participants
- details of procedures, tests, screening to assess trial suitability
- provision of patient information sheet (include as appendix)
- gaining patient consent (how, who, will a witness be present, how long will patient have to decide, what about NESB and other groups such as mentally ill, children etc.)
- details of enrolment procedure

CONSORT CHECKLIST

Criteria 14. Recruitment
Dates defining the periods of
recruitment and follow-up.

Recruitment of centres for multicentre trials

- which centres?
- trial coordinator?
- responsibilities?

EXTRA RESOURCES

In the Protocol Workshop Resource Folder

Aitken L, Gallagher R, Madronio C. Principles of recruitment and retention in clinical trials. *International Journal of Nursing Practice* 2003; **9**:338-346.

Hague W, Gebiski V, Keech A. Recruitment to randomised studies. *MJA* 2003; **178**: 579-581.

YOUR DRAFT PROTOCOL

12. RECRUITMENT

Participant recruitment

Recruitment of centres for multicentre trials

13. DATA MANAGEMENT

Collection

- detailed list of all data to be collected
 - o source of data (patient questionnaires, patient notes, electronic data, procedure)
 - o time point for collection
 - o who will collect data
 - o why data is being collected (e.g. baseline comparison data, main outcome, important prognostic/explanatory variable)
 - o form of data (binary, continuous, time to event etc.)
 - o how will data be measured (standardised tools)
- include a table/diagram describing data collection schedule
- methods for maximising completeness of data (e.g. phoning patients to return postal questionnaires)

CONSORT CHECKLIST

Criteria 15. Baseline data
Baseline demographic and clinical characteristics of each group.

Processing

- describe procedures for data collection and recording (software to be used, location of data etc.)
- methods used to ensure validity and quality of data (e.g. double data entry, cross validation etc.)
- security/storage of data
- records retention – duration and location
- adherence to any relevant legislation
- who is responsible for data collection, recording and quality?

Data collection/processing forms

- include a copy of the forms to be used in the appendix to the protocol?
- develop and pilot test prior to commencement of trial

EXTRA RESOURCES

In the Protocol Workshop Resource Folder

Burgess D, GebSKI V, Keech A. Baseline data in clinical trials. *MJA* 2003; **179**:105-107.

Grimes D, Hubacher D, Nanda K, Schulz K, Moher D, Altman D. The Good Clinical Practice guideline: a bronze standard for clinical research. *Lancet* 2005; **366**:172-174.

Sample data collection/processing forms: (from the PROGRESS Trial)

The data collection forms should be developed to meet the needs of your particular circumstances. Remember that each institution (hospital/university) will have different requirements for ethics approval including the preparation of patient information sheets and consent forms. When designing your data collection forms keep in mind the data entry process and also any processes you develop for checking data entry. Piloting the forms prior to starting the trial will help to iron out any problems with the design.

PROGRESS trial - Trial entry data collection form

PROGRESS trial - Delivery data collection form

PROGRESS trial - Neonatal data collection form

YOUR DRAFT PROTOCOL

13. DATA MANAGEMENT

Collection

Processing

14. DATA ANALYSIS

List variables to be used to assess baseline comparability of randomised groups and how reported

Detailed plan for statistical analyses of primary and secondary outcomes

- summary measures to be reported
- method of analysis (justified with consideration of assumptions of method, structure of data (unpaired, paired, hierarchical etc.)
- plans for handling missing data, non-compliers and withdrawals
- plans for predefined subgroup analyses
- statement that analysis will be intention to treat

Approach for interim analyses and stopping rules

Any non-statistical methods used (e.g. qualitative analyses)

Who will carry out analyses and when?

CONSORT CHECKLIST

Criteria 12. Statistical methods

Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.

Criteria 16. Numbers analyzed

Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (e.g., 10/20, not 50%).

Criteria 17. Outcomes and estimation

For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval).

Criteria 18. Ancillary analyses

Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.

EXTRA RESOURCES

In the Protocol Workshop Resource Folder

Gebski V, Keech A. Statistical methods in clinical trials. *MJA* 2003; **178**:182-185.

O'Connell R, Gebski V, Keech A. Making sense of trial results: outcomes and estimation. *MJA* 2004; **180**:128-130.

Cook D, Gebski V, Keech A. Subgroup analysis in clinical trials. *MJA* 2004; **180**:289-290.

Heritier S, Gebski V, Keech A. Inclusion of patients in clinical trial analysis: the intention-to-treat principle. *MJA* 2003; **179**:438-440.

Fergusson D, Aaron S, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002; **325**:652-654.

Lord S, Gebski V, Keech A. Multiple analyses in clinical trials: sound science or data dredging? *MJA* 2004; **181**:452-454.

Gates S, Brocklehurst P. How should trials including multiple pregnancies be analysed? *BJOG* 2004; **111**:213-219.

Web links

JM Bland, BK Butland, JL Peacock, J Poloniecki, F Reid, P Sedgwick. [Statistics Guide for Research Grant Applicants](#) available at:

http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/guide.cfm

[BMJ Statistics Notes](#) (list available at: <http://www.tufts.edu/~gdallal/bmj.htm>)

14. DATA ANALYSIS

15. DATA MONITORING AND INTERIM ANALYSES

Data monitoring and other quality control measures

- use and role of monitors e.g. DMC, Steering group, and arrangements for monitoring/auditing conduct of research
- assurance on good clinical practice and adherence to research governance guidelines
- detail any other steps taken to ensure quality of research

CONSORT CHECKLIST

Criteria 19. Adverse events
All important adverse events or side effects in each intervention group.

Stopping and discontinuation rules

- define completion and premature discontinuation of trial
- describe procedure regarding decisions on discontinuation (e.g. interim analyses, role of DMC)
- state documentation to be completed if part/all of trial is discontinued
- describe circumstances under which randomisation codes may need to be broken and procedure for this

Handling of adverse events

- definition of serious adverse events expected
- statements about which serious expected adverse events will not be reported
- statement about how non serious adverse events will be recorded and reported
- details of procedures to be followed after adverse event – who has what responsibility
- method and timing for assessing, recording and analysing safety parameters (e.g. interim analyses)
- type and duration of follow-up for subjects after adverse events

EXTRA RESOURCES

In the Protocol Workshop Resource Folder

Dixon D, Freedman R, Herson J, Hughes M, KyungMann K, Silverman M, Tangen C. Guidelines for data and safety monitoring for clinical trials not requiring traditional data monitoring committees. *Clinical Trials* 2006;3:314-319.

Pocock S. Current controversies in data monitoring for clinical trials. *Clinical Trials* 2006; 3:513-521.

Sydes M, Spiegelhalter D, Altman D, Babiker A, Parmar M, DAMOCLES Group. Systematic qualitative review of the literature on data monitoring committees for randomised controlled trials. *Clinical Trials* 2004; 1:60-79.

Grant A. Stopping clinical trials early. *BMJ* 2004; 329:525-526.

Montori V, Devereaux P, Adhikari N, Burns K, Eggert C, Briel M, Lacchetti C, Leung T, Darling E, Bryant D, Bucher H, Schunemann H, Meade M, Cook D, Erwin P, Sood A, Sood R, Lo B, Thompson C, Zhou Q, Mills E, Guyatt G. Randomized trials stopped early for benefit. A systematic review. *JAMA* 2005; 294:2203-2209.

Keech A, Wonders S, Cook D, GebSKI V. Balancing the outcomes: reporting adverse events. *MJA* 2004; 181:215-218.

Web Links

Grant A, Altman D, Babiker A, Campbell M, Clemens F, Darbyshire J, Elbourne D, McLeer S, Parmar M, Pocock S, Spiegelhalter D, Sydes M, Walker A, Wallace S, and the DAMOCLES study group. Issues in data monitoring and interim analysis of trials. *Health Technology Assessment* 2005;9(7). Downloadable from the NHS-HTA website (www.hta.nhsweb.nhs.uk/)
Extract- Appendix 1:Statistical approaches to data monitoring in Resource Folder

YOUR DRAFT PROTOCOL

15. DATA MONITORING AND INTERIM ANALYSES

Data monitoring and other quality control measures

Stopping and discontinuation rules

15. DATA MONITORING AND INTERIM ANALYSES continued...

Stopping and discontinuation rules continued

Handling of adverse events

Your notes

16. ETHICAL CONSIDERATIONS

Ethical considerations

- approvals from relevant groups (i.e. Ethics committee/s)
- informed consent (append information sheet and IC form)
- allowances for special groups (NESB, children, mentally ill)
- patient withdrawal/discontinuation
- trial monitoring

EXTRA RESOURCES

In the Protocol Workshop Resource Folder

Green J, Duncan R, Barnes G, Oberklaid F. Putting the “informed” into “consent”: A matter of plain language. *Journal of Paediatrics and Child Health* 2003; **39**:700-703.

Yusuf S, Bosch J. Independent design and conduct of clinical trials. *Clinical Trials* 2006; **3**:503-507.

Web Links

Edwards S, Lilford R, Brauholtz D, Jackson J, Hewison J, Thornton J. Ethical issues in the design and conduct of randomised controlled trials. *Health Technology Assessment* 1998; **2**(15). Downloadable from the NHS-HTA website (www.hta.nhsweb.nhs.uk/)

YOUR DRAFT PROTOCOL

16.ETHICAL CONSIDERATIONS

17. RESOURCES AND STAFFING REQUIREMENTS

Budget

- Personnel
- Equipment
- Maintenance
- Travel

Justification of budget

- Funding available

Staffing requirements

- Job description of personnel required.

EXTRA RESOURCES

Web links

Budget mechanism for Project Grant funding from NHMRC

<http://www.nhmrc.gov.au/funding/apply/granttype/projects/budget.htm>

Costing research projects - advice from University of Sydney Research Office

<http://www.usyd.edu.au/ro/applications/budget.shtml>

Most universities have specific guidelines about how to calculate direct and indirect research costs, how to manage research contracts involving commercial partners and how to meet University guidelines for cost recovery where applicable. This information can be accessed by visiting the research branch/office pages of the relevant university website.

YOUR DRAFT PROTOCOL

17. RESOURCES AND STAFFING REQUIREMENTS

Budget

Justification of budget

Staffing requirements

18. IMPLEMENTATION PLAN

Organisation

Responsibilities – who will do what?

Timetable

Pilot studies required

Funding

EXTRA RESOURCES

In the Protocol Workshop Resource Folder

Koren G. How to increase your funding chances: common pitfalls in medical grant applications. *Canadian Journal of Clinical Pharmacology* 2005; 12:e182-e185.

Inouye S, Fiellen D. An evidence-based guide to writing grant proposals for clinical research. *American College of Physicians* 2005; 142:274-282.

Morley C, Middleton P, Toohar R. *WOMBAT Maternal and Perinatal Toolkit - Tips for writing grant submissions*. Last revised Jan 2007.

Web Links

Writing grant submissions - links page from University of Adelaide Research Branch
<http://www.adelaide.edu.au/rb/funding/writing.html>

YOUR DRAFT PROTOCOL

18. IMPLEMENTATION PLAN

Organisation

Responsibilities

Timetable

18. IMPLEMENTATION PLAN continued...

Pilot studies required

Funding required

19. REFERENCES

It is probably a good idea to note any important references as you are writing your protocol so that you don't have to hunt them down after it is complete. If there are a large number of references we recommend using reference management software (such as Reference Manager or Endnote).

References

References

GENERAL RESOURCES

Books

Schulz K, Grimes D. *The LANCET Handbook of Essential Concepts in Clinical Research*. Philadelphia, USA: Elsevier Ltd. 2006.

Meinert C. *Clinical trials. Design, conduct and analysis*. New York: Oxford University Press, 1986.

Web Links

EMB Glossary (Uni Toronto)

<http://www.cebm.utoronto.ca/glossary/index.htm#top>

Netting the evidence (Uni Sheffield)

<http://www.shef.ac.uk/scharr/ir/netting/>

Users guide to the medical literature

<http://www.cche.net/usersguides/main.asp>

Centre for Evidenced-Based Medicine (Oxford)

www.cebm.net

In the Protocol Workshop Resource Folder

Henderson-Smart D, Osborn D, Evans N, Beeby P, Jeffery H. Do we practice evidence-based care in our neonatal intensive care units? *Clinics in Perinatology* 2003; **30**:333-342.

Grimes D, Schulz K. An overview of clinical research: the lay of the land. *The Lancet* 2002; **359**:57-61.

Dodd J, Crowther C. Cochrane reviews in pregnancy: the role of perinatal randomised trials and systematic reviews in establishing evidence. *Seminars in Fetal and Neonatal Medicine* 2006; **11**:97-103.

Kramer M. Randomised trials and public health interventions: time to end the scientific double standard. *Clinics in Perinatology* 2003; **30**: 351-361.

Glud L. Bias in clinical intervention research. *American Journal of Epidemiology* 2006; **163**:493-501.

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